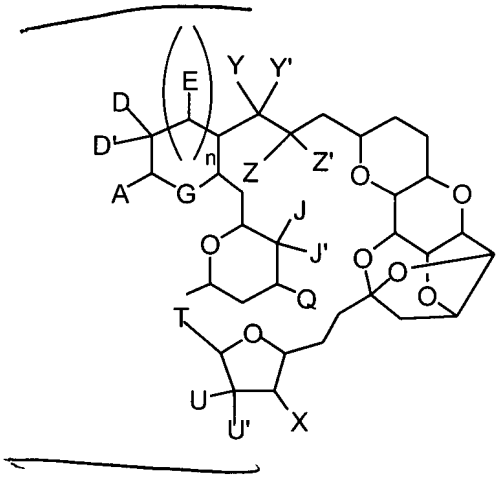
CLAIMS

1. A compound having the formula:



T1340

wherein A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, said skeleton being unsubstituted or having between 1 and 10 substituents, inclusive, independently selected from cyano, halo, azido, oxo, and Q_1;

each Q_1 is independently selected from OR_1, SR_1, SO_2R_1, OSO_2R_1, NR_2R_1, $NR_2(CO)R_1$, $NR_2(CO)(CO)R_1$, $NR_4(CO)NR_2R_1$, $NR_2(CO)OR_1$, $(CO)OR_1$, $O(CO)R_1$, $(CO)NR_2R_1$, and $O(CO)NR_2R_1$;

each of R_1, R_2, R_4, R_5, and R_6 is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{6-10} aryl, C_{6-10} haloaryl, C_{6-10} hydroxyaryl, C_{1-3} alkoxy-C_6 aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{1-6} alkyl-C_{6-10} aryl, C_{6-10} haloaryl-C_{1-6} alkyl, C_{1-6} alkyl-C_{6-10} haloaryl, (C_{1-3} alkoxy-C_6 aryl)-C_{1-3} alkyl, C_{2-9} heterocyclic radical, C_{2-9} heterocyclic radical-C_{1-6} alkyl, C_{2-9} heteroaryl, and C_{2-9} heteroaryl-C_{1-6} alkyl;

each of D and D' is independently selected from R_3 and OR_3, wherein R_3 is H, C_{1-3} alkyl, or C_{1-3} haloalkyl;

n is 0 or 1;

E is R_5 or OR_5;

G is O, S, CH_2, or NR_6;

134

each of J and J' is independently H, C_{1-6} alkoxy, or C_{1-6} alkyl; or J and J' taken together are $=CH_2$ or –O-(straight or branched C_{1-5} alkylene)-O-;

Q is C_{1-3} alkyl;

T is ethylene or ethenylene, optionally substituted with $(CO)OR_7$, where R_7 is H or C_{1-6} alkyl;

each of U and U' is independently H, C_{1-6} alkoxy, or C_{1-6} alkyl; or U and U' taken together are $=CH_2$ or –O-(straight or branched C_{1-5} alkylene)-O-;

X is H or C_{1-6} alkoxy;

each of Y and Y' is independently H or C_{1-6} alkoxy; or Y and Y' taken together are =O, $=CH_2$, or –O-(straight or branched C_{1-5} alkylene)-O-; and

each of Z and Z' is independently H or C_{1-6} alkoxy; or Z and Z' taken together are =O, $=CH_2$, or –O-(straight or branched C_{1-5} alkylene)-O-;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein n is 0.

3. The compound of claim 1, wherein each of D and D' is independently selected from R_3, C_{1-3} alkoxy, and C_{1-3} haloalkyloxy.

4. The compound of claim 1, wherein R_5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{6-10} aryl, C_{6-10} haloaryl, C_{6-10} hydroxyaryl, C_{1-3} alkoxy-C_6 aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{1-6} alkyl-C_{6-10} aryl, C_{6-10} haloaryl-C_{1-6} alkyl, C_{1-6} alkyl-C_{6-10} haloaryl, (C_{1-3} alkoxy-C_6 aryl)-C_{1-3} alkyl, C_{2-9} heterocyclic radical, C_{2-9} heterocyclic radical-C_{1-6} alkyl, C_{2-9} heteroaryl, and C_{2-9} heteroaryl-C_{1-6} alkyl.

5. The compound of claim 1, wherein A comprises a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, said skeleton having at least one substituent selected from cyano, halo, azido, oxo, and Q_1;

each Q_1 is independently selected from OR_1, SR_1, SO_2R_1, OSO_2R_1, NR_2R_1, $NR_2(CO)R_1$, and $O(CO)NR_2R_1$;

n is 0;

G is O;

J and J' taken together are $=CH_2$;

Q is methyl;

T is ethylene;

U and U' taken together are $=CH_2$;

X is H;

each of Y and Y' is H; and

Z and Z' taken together are =O or $=CH_2$.

6. The compound of claim 1, wherein each Q_1 is independently selected from OR_1, SR_1, SO_2R_1, OSO_2R_1, $NH(CO)R_1$, $NH(CO)(CO)R_1$, and $O(CO)NHR_1$;

each R_1 is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_6 aryl, C_6 haloaryl, C_{1-3} alkoxy-C_6 aryl, C_6 aryl-C_{1-3} alkyl, C_{1-3} alkyl-C_6 aryl, C_6 haloaryl-C_{1-3} alkyl, C_{1-3} alkyl-C_6 haloaryl, (C_{1-3} alkoxy-C_6 aryl)-C_{1-3} alkyl, C_{2-9} heterocyclic radical, C_{2-9} heteroaryl, and C_{2-9} heteroaryl-C_{1-6} alkyl;

one of D and D' is methyl or methoxy, and the other is H;

n is 0;

G is O;

J and J' taken together are $=CH_2$;

Q is methyl;

T is ethylene;

U and U' taken together are $=CH_2$;

X is H;

each of Y and Y' is H; and

Z and Z' taken together are =O.

7. The compound of claim 6, wherein A has at least one substituent selected from hydroxyl, amino, azido, halo, and oxo.

8. The compound of claim 7, wherein A comprises a saturated hydrocarbon skeleton having at least one substituent selected from hydroxyl, amino and azido.

9. The compound of claim 8, wherein A has at least two substituents independently selected from hydroxyl, amino, and azido.

10. The compound of claim 8, wherein A has at least two substituents independently selected from hydroxyl and amino.

11. The compound of claim 8, wherein A has at least one hydroxyl substituent and at least one amino substituent.

12. The compound of claim 8, wherein A has at least two hydroxyl substituents.

13. The compound of claim 8, wherein A comprises a C_{2-4} hydrocarbon skeleton.

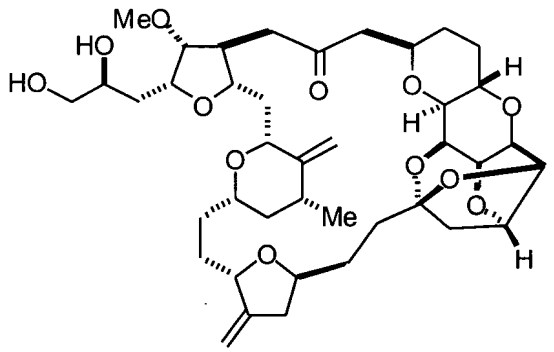
14. The compound of claim 8, wherein A comprises a C_3 hydrocarbon skeleton.

15. The compound of claim 13, wherein A has an (S)-hydroxyl on the carbon atom alpha to the carbon atom linking A to the ring containing G.

16. The compound of claim 6, wherein A comprises a C_{1-6} saturated hydrocarbon skeleton having at least one substituent selected from hydroxyl and cyano.

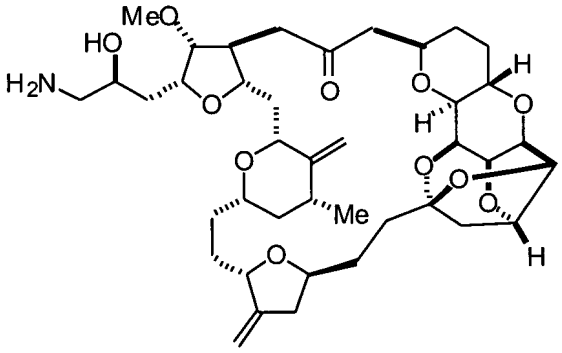
17. The compound of claim 6, wherein Q_1 is independently selected from OR_1, SR_1, SO_2R_1, and OSO_2R_1 where each R_1 is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_6 aryl, C_6 haloaryl, C_{1-3} alkoxy-C_6 aryl, C_6 aryl-C_{1-3} alkyl, C_{1-3} alkyl-C_6 aryl, C_6 haloaryl-C_{1-3} alkyl, C_{1-3} alkyl-C_6 haloaryl, and (C_{1-3} alkoxy-C_6 aryl)-C_{1-3} alkyl.

18. The compound of the following structure



T 1380

19. The compound of the following structure



T1387

and pharmaceutically acceptable salts thereof.

20. A method for identifying an agent that induces a sustained mitotic block in a cell after transient exposure of said cell to said agent, said method comprising the steps of:

(a) incubating a first cell sample with a predetermined concentration of a test compound

138

for a time interval between that sufficient to empty the G_1 population and that equivalent to one cell cycle;

(b) substantially separating said test compound from said first cell sample;

(c) incubating said first sample in media free of said test compound for a time interval sufficient to allow at least 80% of the cells released from the mitotic block induced by a highly reversible mitotic inhibitor to complete mitosis and return to the G_1 phase; and

(d) measuring the percentage of transiently-exposed cells from step (c) that have completed mitosis and returned to the G_1 phase.

21. The method of claim 20, further comprising the steps of:

(e) incubating a second sample of cells with a concentration of said test compound less than or equal to that used in step (a) for a time interval between that sufficient to empty the G_1 population and that equivalent to one cell cycle;

(f) measuring the percentage of cells from step (e) that have completed mitosis and have returned to the G_1 phase; and

(g) determining the relative reversibility of said test compound by relating the measurement of step (d) and the measurement of step (f).

#9

C1

THIS APPLICATION CLAIMS BENEFIT OF PROVISIONAL APPLICATION SERIAL NUMBER ~~60~~ 60/049,482 FILED 6/17/98.

140